Remarks

Reconsideration of the application is respectfully requested in view of the following remarks. Claims 1-6, 8-51, and 61-65 remain in this application. Claim 1 has been amended and new claims 71-96 have been added. No claims have been allowed. Claims 1, 29, 31, 33, 36, 47, 50, 61, 64, and 71 are independent. Claims 52-53, 66-67, and 68-70 have been canceled without prejudice (e.g., to pursuing in a continuation or divisional application).

Withdrawn Claims 68-70

Claims 68-70 have been canceled.

Examiner Interview

Applicants wish to thank the Examiner and her Supervisor for their time during a personal interview with the undersigned agent and Greg Maurer on December 2, 2004. Agreement was not reached. Due to disagreement regarding the claims, Applicants have reviewed the specification and present claims 71-96, composed anew in light of the interview. As discussed in the interview, Applicants provide citations indicating where support for the claim language can be found in the specification.

Patentability of New Claims 71-96

New claims 71-96 find support in the specification as detailed below. These claims each recite patentably distinct subject matter not taught or suggested by previously cited art.

During the interview, concerns were voiced over enablement, particularly relating to comparing different model types, predicting gene expression for different genes, and comparing models based on different data. To find common ground for allowable subject matter, Applicants have included various language in the claim to address these concerns. Because Applicant was cautioned to find clear support in the Application, Applicants now present pinpoint citations for exemplary support in the specification.

Claim 71 is directed to a method comprising constructing multivariate nonlinear models, measuring effectiveness of the models, ordering, and presenting results. Support for constructing the models can be found in the Application, for example, at page 13, line 3 through page 14, line 11, including FIG. 8 and Tables 1 and 2. For purposes of emphasizing

language clarity, the claim recites two models, but, as indicated in FIG. 8 and the accompanying text, a plurality of models can be constructed.

The text of the application referring to FIG. 8 at page 13, lines 11-12 describe that a multivariate nonlinear model (e.g., a first model) is constructed at 812 of FIG. 8 "based on data from the experiments" where the model has "predictive elements as inputs and the predicted gene as the output." At 816 of FIG. 8, the "effectiveness of the model in predicting expression of the predicted gene is measured." (see page 13, lines 12-14). Depending on the outcome of action 820 of FIG. 8, another set of predictive elements[1] for the predicted gene is designated at 808 of FIG. 8 and another (e.g., second or subsequent) model is constructed and its effectiveness measured. Tables 1 and 2 give examples of how the method could work. Table 1 includes obtained expression data for multiple genes and Table 2 includes the results for multiple models generated using different permutation subsets of predictive elements. The Application thus supports the constructing actions of the claim.

At page 17, lines 3 et seq., the Application states that "An exemplary user interface for presenting data similar to that of Table 2 is shown in the display region 1102 of FIG. 11." Further description of FIG. 11 at page 17, lines 21 et seq. indicates, "as shown, the bars are ordered (i.e. the more effective models are shown at the top)." The description on page 17 of the specification describing FIG. 11 thus supports the ordering and presenting actions of the claim. Page 17, lines 7-8, describe, "Effectiveness of the model is indicated by the size of the bar."

Claim 71 further recites "wherein the first . . . and the second multivariate nonlinear model are of a same model type." The abstract describes, "Various types of models, including full-logic or neural networks can be constructed." In the Summary on page 3, the Application indicates at line 11, "One implementation uses a full-logic multivariate nonlinear model," and at line 15, "Another implementation uses a neural network-based multivariate nonlinear model." Thus, the Application supports language reciting the same model type.

Claim 71 further recites "wherein the first . . . and the second multivariate nonlinear model predict the gene expression level for the candidate gene." Examples of models predicting gene expression for the same (e.g., "target") gene are found in the description of

[1] Page 13, line 9 describes examples of predictive elements (obtained expression data for genes, experimental/biological conditions, etc.).

FIG. 8 at page 13, line 7: "At 802, one of the observed genes is designated as a predicted gene," which is tied to the above constructing language.

Claim 71 further recites "wherein the first . . . and the second multivariate nonlinear model are constructed via gene expression data from a same set of experiments." Again, the description of FIG. 8 at page 13, line 10 describes that the models are constructed "based on data from the experiments." In the example, various gene expression data (e.g., Table 1) from the same *k* experiments is used to construct the models.

Accordingly, the Application contains sufficient (and sufficiently linked) language which would convey to one of skill in the art that the inventors were in possession of the invention recited by claim 71. Further, the claim contains sufficient language that ties it to a clearly enabled implementation of the technology. For at least these reasons, new claims 71-96 are allowable under § 112, ¶ 1. Dependent claims 72-96 (many of which mimic original dependent claims 2-30) recite additional features that are patentably distinct, novel and non-obvious combinations that are also allowable at this time.

Patentability of Claims 1-6, 8-51, and 61-65 under § 112, ¶ 1

In the interest of preserving the other claims for future prosecution, Applicants respond to the claim rejections set forth in the Action. The Action rejects claims 1-6, 8-51, and 61-65 as containing subject matter not described in such a way as to reasonably convey to one of skill in the art that the inventors had possession of the claimed invention. Applicants respectfully disagree with the rejection.

First, the Action asserts that in order to practice the claimed combinations, relative gene relatedness must be quantified. The Action concludes that undue experimentation must be performed to achieve such quantification. Applicants point out that the Application describes that relatedness can be quantified by measuring the effectiveness of a model. Various examples are shown in the Application, so the claims are enabled.

Applicants continue by addressing the eight factors of *In re Wands.*

1. Quantity of Experimentation Necessary

Applicants respectfully disagree with the conclusion that much experimentation would be necessary. Rather, as described in the Application, multiple nonlinear models can be constructed for predicting a gene expression level for a candidate gene from permutation

subsets of genes selected out of a set of genes for which observed gene expression levels are available. The more accurate a model is in predicting the gene expression level for the candidate gene, the higher relatedness (e.g., codetermination) between the genes that comprise the permutation subset and the candidate gene relative to the relatedness between the genes that comprise a permutation subset and the candidate gene in a less accurate model. Applicants describe gene relatedness on page 6, line 20 as " includes genes having any of a variety of relationships, including coexpressed genes, coregulated genes, and codetermined genes. The mechanism of the relationship need not be a factor in determining relatedness."

2. Amount of Direction or Guidance Presented

Examiner cites page 11, line 18 to page 12, line 4 of the specification as reciting steps that are not reflected in the instant claims. Enablement does not require that the claim provide guidance. Guidance in the specification is sufficient. In the instant claims, the *exact mechanism responsible for* relatedness of a gene to individual subset combinations is not determined. Rather it is asserted that the more accurate a model is in predicting the gene expression level for the candidate gene indicates a higher relatedness between the genes that comprise the permutation subset and the candidate gene *relative* to the lower relatedness between the genes the comprise a permutation subset and the candidate gene in a less accurate model.

The method can indicate which genes are codetermined. The method increases the speed of identifying new components of already identified processes and of finding unexpected links between processes not previously known to coordinated. It is expected that changes in mRNA levels will, for some subsets of genes, reflect their level of functional coupling. If the relative abundance of the messages for these genes is observed over a wide sampling of cell states, then it will be possible to rank the tightness of coupling between genes. This can be accomplished by determining how accurately the states of a set of genes predict the state of some other gene. The higher the degree of relationship, (e.g., the more codetermined the set of genes) the more accurate the prediction. The method allows the ability to discern and rank connections independent of a model of interaction or complete information.

The Action further asserts that the limitations of the non-linear model are not fully described. As described in the specification, "A variety of multivariate nonlinear models for predicting gene expression are possible" (see page 19, lines 15-16). An overview of exemplary multivariate nonlinear models for predicting gene expression is described in the specification starting on page 14, line 12 and continuing through page 16, line 30. In particular exemplary full-logic and neural network multivariate nonlinear models are described in the specification beginning on page 19, line 17 and continuing through page 28, line 11.

Construction of full-logic and neural network multivariate nonlinear models is enabled.

3. Presence or Absence of Working Examples

Applicants agree with the Examiner that the specification provides working examples of using the particular method to determine relatedness of a set of genes beginning on page 28, line 12 and continuing to page 33, line 4. Applicants respectfully disagree with the Examiner that the instant claims need to reflect various steps from the specification. The claim need not provide a working example; a working example in the specification is sufficient. Starting on page 31 and FIG. 19 through page 33 and FIG. 23, examples for implementing the actions in the instant claims of constructing multiple multivariate nonlinear models for predicting a gene expression level for a candidate gene from a permutation subset are described.

4. Nature of the Invention

The claims include those drawn to a method for predicting the relatedness of a permutation subset of genes to a candidate gene relative to the relatedness of another permutation subset of genes to the candidate gene.

5. State of the Prior Art AND 7. Predictablity/Unpredictability of the Art

Applicants respectfully agree with the Examiner that "the prior art provides no recognized model of a computer implemented method for quantifying relative gene relatedness using the steps of the instant invention."

6. Relative Skill of Those in the Art

Applicants respectfully agree with the Examiner that "the skill of those in the art of bioinformatics in high."

8. Breadth of the Claims

The claims are of varying breadth.

On balance, due to the Applicants' disagreement with the Action's assertion that working examples should be reflected in the claims, Applicants believe undue experimentation would not be required to make and use the invention as set forth in the claims.

Patentability of Claims 1-6, 8-51, and 60-65 under § 112, ¶ 2

The Action has objected to the language "selecting a plurality of selected" in claim 1. Applicants have clarified to "selecting a plurality of subset gene combinations of the plurality of candidate genes."

The Action has further objected to claim 1 that "there are no limitations on the non-linear model." Claim 1 has been amended to read, "multivariate nonlinear model" to clarify. As described in the specification, "A variety of multivariate nonlinear models for predicting gene expression are possible" (see page 19, lines 15-16). An overview of exemplary multivariate nonlinear models for predicting gene expression is described in the specification starting on page 14, line 12 and continuing through page 16, line 30. In particular, exemplary full-logic and neural network multivariate nonlinear models are described in the specification beginning on page 19, line 17 and continuing through page 28, line 11. Dependent claims 10 (full-logic), 16-19 (truth table) and 20-26 (neural network) further describe the non-linear model.

The Action has objected to the recitation of "predictive element" in claim 15. Claim 15 has been amended to depend from claim 3, which recites "predictive elements."

Use of the Word "Related"

During discussions with the Examiner and her Supervisor, disagreement has arisen over use of the word "related" and whether it is enabled in the application. For consideration by the Examiner, Applicants cite U.S. Publication No. US 2003/0 152 969 ("Quake") in an IDS herewith. Based on the PAIR system, Applicants believe that Quake's claim 1 has been allowed by the Office. Although Quake appears not to be prior art and holds no legal authority, it is presented for comparison as an example of claims that have been allowed by the Office that use the word "related" with respect to genes.

Conclusion

The claims in their present form should now be allowable. Such action is respectfully requested.

Respectfully submitted,

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